

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 39/395 // (A61K 39/395, 31:34, 31:415, 33:06, 33:10)	A1	(11) International Publication Number: WO 00/62806 (43) International Publication Date: 26 October 2000 (26.10.00)
(21) International Application Number: PCT/US99/08578 (22) International Filing Date: 19 April 1999 (19.04.99) (71)(72) Applicant and Inventor: WEISBART, Richard [US/US]; 9621 Lockford Street, Los Angeles, CA 90035 (US). (74) Agents: DIGIGLIO, Frank, S. et al.; Scully, Scott, Murphy & Presser, 400 Garden City Plaza, Garden City, NY 11530 (US).		(81) Designated States: CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: TREATMENT OF ADULT RHEUMATOID ARTHRITIS BY ORAL ADMINISTRATION OF POOLED HUMAN IMMUNOGLOBULIN AND AN ANTACID (57) Abstract Pooled human immunoglobulin and an antacid may be administered orally to adult rheumatoid arthritis patients to treat the rheumatoid arthritic condition of those patients. Oral administration of pooled human immunoglobulin in conjunction with an antacid results in significant clinical improvement in the level of disease activity in patient with adult rheumatoid arthritis.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

TREATMENT OF ADULT RHEUMATOID ARTHRITIS BY
ORAL ADMINISTRATION OF POOLED HUMAN
IMMUNOGLOBULIN AND AN ANTACID

5

10

FIELD OF THE INVENTION

The present invention relates to the treatment of adult rheumatoid arthritis. More particularly, the invention relates to the treatment of adult rheumatoid arthritis by oral administration of a pharmaceutical composition comprising pooled human immunoglobulin in conjunction with an antacid.

20

BACKGROUND OF THE INVENTION

Adult rheumatoid arthritis is a systematic inflammatory disease that commonly affects the joints, particularly those of the hands and feet. The onset of rheumatoid arthritis can occur slowly, ranging from a few weeks to a few months, or the condition can surface rapidly in an acute manner.

25

Today, over 2,500,00 individuals are diagnosed with adult rheumatoid arthritis in the United States alone (1% of population), with some statistics indicating that from 6.5 to 8 million adults are potentially afflicted with the disease. Women are affected 2-3 times more often than men. Adult rheumatoid arthritis can

30

occur in young adults and typically will increase in incidence with age.

5 The classic early symptoms of adult rheumatoid arthritis include stiffness, tenderness, fever, subcutaneous nodules, achy joints, and fatigue. The joints of the hands, feet, knees and wrists are most commonly affected, with eventual involvement of the hips, elbows and shoulders. As the joints stiffen and swell, any type of motion becomes very painful and difficult.

10 The more severe cases of adult rheumatoid arthritis can lead to intense pain and eventual joint destruction. Some 300,000 bone and joint replacement surgical procedures are performed annually in an effort to alleviate the pain and mobility loss resultant from

15 arthritis related joint destruction.

 Adult rheumatoid arthritis and juvenile rheumatoid arthritis are two different diseases. Juvenile rheumatoid arthritis is most common in children and includes eight different forms of disease. One form

20 of juvenile rheumatoid arthritis, Rf-positive polyarticular juvenile rheumatoid arthritis, bears some resemblance to adult rheumatoid arthritis. However, only about 40% of all juvenile rheumatoid arthritis cases are polyarticular and, of these, only about 5-10% are

25 rheumatoid factor (Rf) positive. Therefore, only 2-4% of juvenile rheumatoid arthritis patients suffer from Rf-positive polyarticular juvenile rheumatoid arthritis.

 Juvenile rheumatoid arthritis is characterized by abnormal T and B cell function and selective IgA

30 deficiency. Adult rheumatoid arthritis is a disease identified by the presence of auto-antibodies including certain characteristic rheumatoid factors. The

immunogenetic associations, clinical course, and functional outcome of juvenile rheumatoid arthritis are quite different from adult-onset rheumatoid arthritis. Pediatric Rheumatic Diseases In: Primer on the Rheumatic Diseases, 11ed. 1997 (incorporated herein by reference).

The effective treatment of adult rheumatoid arthritis has generally employed a combination of medication, exercise, rest and proper joint protection therapy. The therapy for a particular patient depends on the severity of the disease and the joints that are involved. Aspirin is widely used for pain and to reduce inflammation. In addition to aspirin, non-steroidal anti-inflammatory drugs, corticosteroids, gold salts, anti-malarials and systemic immuno-suppressants are widely used in moderate to advanced cases. The use of steroids and immunosuppressants, however, has significant risks and side effects both in terms of toxicity and vulnerability to potentially lethal conditions such as infection and malignancy. Thus, there exists a need for a method of treating adult rheumatoid arthritis which does not entail the potentially lethal side effects associated with the treatments described above.

"Superantigens" have been considered as stimulants of the immune system in various autoimmune diseases including rheumatoid arthritis. Herman, A., et al. (1991) Annu. Rev. Immunol. 9:745-772; Drake, C.G. and Kotzin, B.L. (1992) J. Clin. Immunol. 12:149-162 (incorporated herein by reference). The gastrointestinal tract may be the site of immunologic stimulation by superantigens. There may be a defect in the ability of patients with adult rheumatoid arthritis to produce antibodies with the correct neutralizing specificities.

One approach to treating rheumatoid arthritis is to orally administer cow's milk to patients. See U.S. Patent No. 4,732,757 (Stolle, et al.). Stolle, et al. disclose that hyperimmunized milk containing a high titer of specific antibodies from animals actively and artificially immunized and boosted with large amounts of purified antigen is useful to treat rheumatoid arthritis. The drawbacks to this approach are several-fold. The cow donors pool must be specifically and actively immunized to a small subset of antigens. In addition, some patients have adverse reactions to consumption of bovine milk. Moreover, cow's milk does not contain the entire spectrum of antibodies present in a human. Furthermore, the effects of hyperimmune milk on inflammatory processes, such as rheumatoid arthritis, has largely been discarded. See Ormrod and Miller (1991) Agents and Actions, 32(3/4):160-166.

Another approach to the treatment of autoimmune diseases, of which rheumatoid arthritis is an example, is tolerization of the patient suffering from the autoimmune disease to the particular autoantigen(s) involved in the disease. In Weiner, et al., Science 259:1321-1324 (1993) (incorporated herein by reference), multiple sclerosis patients were orally administered bovine myelin protein, which contains two multiple sclerosis autoantigens. In Trentham, et al., Science 261:1727-1730 (1993) (incorporated herein by reference), rheumatoid arthritis patients were orally administered collagen, a presumed autoantigen. One drawback to tolerization is the identification of the correct autoantigen to which tolerance is to be induced.

In view of the unsuccessful and disadvantageous modalities currently employed there is a continued need to develop effective methods and compositions for the treatment of adult autoimmune rheumatoid arthritis.

5

SUMMARY OF THE INVENTION

The present invention is directed to a method for treating an adult rheumatoid arthritis patient by orally administering an amount of pooled human immunoglobulin in conjunction with an antacid which is sufficient to provide a clinically observable improvement in a patient's rheumatoid arthritic condition. The present invention is based on the discovery that the oral administration of pooled human immunoglobulin in conjunction with antacids, to patients with adult rheumatoid arthritis results in a significant clinical improvement in the rheumatoid arthritic condition of the patient. The present invention is also based on the discovery that there are no toxic effects of orally administered pooled human immunoglobulin in conjunction with an antacid to adult rheumatoid arthritis patients.

10
15
20

BRIEF DESCRIPTION OF THE FIGURES

25

Fig. 1 is a Joint Tenderness and Swelling graph for patient GEC who was treated with oral gammaglobulin in combination with cimetidine.

30

Fig. 2 is a Joint Tenderness and Swelling graph for patient RR who was treated with oral gammaglobulin in combination with cimetidine.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

5 The present invention concerns a method for
treating a patient with adult rheumatoid arthritis. This
is accomplished by orally administering pooled human
immunoglobulin in conjunction with an antacid. An
immunoglobulin, introduced into the acidic environment of
the human stomach, may suffer inactivation. To alleviate
such inactivation and/or provide increased therapeutic
10 efficacy, the pooled human immunoglobulin employed in the
method of the present invention is administered in
conjunction with an antacid. The present invention also
contemplates pharmaceutical compositions comprising
pooled human immunoglobulin and an antacid. While not
15 wishing to be bound to a particular mechanism, the acid
blocker may neutralize the otherwise acidic character of
the gut thereby shielding the immunoglobulin from
digestion in the stomach. Alternatively, the acid-
blocker and immunoglobulin may synergistically provide
20 remediation of arthritis symptoms by suppressing
inflammatory mediators or immune-mediated inflammation.

 Surprisingly, in accordance with the present
invention it has now been discovered that encapsulated
immunoglobulin IgG, intended to avoid the acidic
25 character of the stomach and provide sustained release in
the intestines, does not manifest any noticeable
improvement relative to uncoated IgG. This determination
demonstrates that the antacid is not merely shielding the
immunoglobulin from the gut, but acting synergistically
30 to improve the effectiveness of the immunoglobulin.
Accordingly, the present invention contemplates
pharmaceutical compositions containing pooled

immunoglobulin and an antacid which provides increased efficacy relative to pooled human immunoglobulin administered alone.

5 As used herein, the term "pooled human immunoglobulin" refers to an immunoglobulin composition containing polyclonal antibodies obtained from the plasma of thousands of human donors. The polyclonal antibodies may include IgG, IgA, IgM, etc. or fragments thereof. A preferred polyclonal antibody is IgG. A preferred
10 immunoglobulin composition contains at least about 90% IgG polyclonal antibodies and trace amounts of other polyclonal antibodies such as, for example, IgA and IgM. Examples of pooled human immunoglobulin compositions useful in accordance with the present invention include, but are not limited to, Sandoglobulin®, Gammagard®,
15 Gamimune® and Gammar®. In accordance with the present invention any pooled human immunoglobulin can be used.

"Antacid" when used herein denotes an H₂-blocker or acid blocker or other acid neutralizing agent
20 which neutralizes and/or significantly reduces the acidic content of the gut. A preferred antacid useful in accordance with the teachings of the present invention is cimetidine.

A "clinically observable improvement" when used
25 herein refers to a significant subjective remediation of symptoms associated with the patient's rheumatoid arthritic condition including, but not limited to, tender joint(s), swollen joint(s) and stiffness assessments. Significant subjective remediation of symptoms denotes a
30 patient's self-assessment or a physician's assessment of stiffness, joint tenderness, swelling and the like. For example, an observable difference in swelling or

tenderness in even one arthritic joint is significant.
Absence of swelling or tenderness in a previously
affected joint is most significant.

Another aspect of the present invention
5 provides a pharmaceutical composition comprising pooled
human immunoglobulin, an antacid and a pharmaceutically
acceptable carrier. In a preferred embodiment the
composition comprises Sandoglobulin®, cimetidine and a
pharmaceutically acceptable carrier. As used herein,
10 "pharmaceutically acceptable carrier" includes any and
all solvents, dispersion media, coatings, antibacterial
and antifungal agents, isotonic and absorption delaying
agents, and the like. The use of such media and agents
for pharmaceutical active substances is well known in the
15 art. Except insofar as any conventional media or agent
is incompatible with the active ingredients, its use in
the therapeutic compositions is contemplated.

"Treating" as used herein includes measures to
ameliorate, suppress, mitigate or eliminate the clinical
20 symptoms after the onset (i.e., clinical manifestation)
of adult rheumatoid arthritis.

"Oral" administration as used herein includes
oral, enteral or intragastric administration.

"In conjunction with" as used herein means
25 before, substantially simultaneously with or after oral
administration of antacid. Of course, the immunoglobulin
composition can not precede or follow administration of
an antacid by so long an interval of time that the
relevant effects of the substance administered first have
30 expired. Therefore, the immunoglobulin composition
should usually be administered within a therapeutically
effective time. By "therapeutically effective time," as

used herein, is meant a time frame in which the antacid or immunoglobulin is still active within the patient.

In a preferred embodiment, the pooled human immunoglobulin is produced by cold alcohol (e.g., ethanol) fractionation from the plasma of thousands of human volunteers.

In another preferred embodiment, pooled human immunoglobulin is purchased from Novartis Pharmaceuticals, where it is sold under the name Immune Globulin Intravenous (Human) Sandoglobulin®. Sandoglobulin® is a sterile, highly purified polyvalent antibody product containing, in concentrated form, all the IgG antibodies which regularly occur in the donor population. This immunoglobulin preparation is produced by cold alcohol fractionation from the plasma of over 16,000 volunteer donors. Sandoglobulin® (IGIV) is made suitable for intravenous use by treatment at acid pH in the presence of trace amounts of pepsin. The preparation contains at least 96% of IgG and with a neutral unbuffered diluent has a pH of 6.6 ± 0.2 . Most of the immunoglobulins are monomeric (7 S) IgG; the remainder consists of dimeric IgG and a small amount of polymeric IgG, traces of IgA and IgM and immunoglobulin fragments [Römer J, Späth PJ: Molecular composition of immunoglobulin preparations and its relation to complement activation, in Nydegger UE (ed): Immunohemotherapy: A Guide to Immunoglobulin Prophylaxis and Therapy. London, Academic Press, 1981, p. 123.]. The distribution of the IgG subclasses corresponds to that of normal serum. Final container lyophilized units are prepared so as to contain 1, 3 or 6 g protein with 1.67 g sucrose and less than 20 mg NaCl per gram of

protein. The lyophilized preparation is devoid of any preservatives and may be reconstituted with sterile water.

5 In still another preferred embodiment, pooled human immunoglobulin is purchased from the Baxter Healthcare Corporation, where it is sold under the name Immune Globulin Intravenous (Human) Gammagard®. Gammagard® is a sterile, freeze dried preparation of highly purified immunoglobulin G (IgG) derived from large
10 pools of human plasma. Gammagard® is manufactured by cold ethanol fractionation. Gammagard® contains at least about 90% IgG and trace amounts of IgA and IgM. Gammagard®, reconstituted to 5%, contains a physiological concentration of sodium chloride (approx. 8.5 mg/mL) and
15 has a pH of 6.8 ± 0.4 . The distribution of IgG subclasses is similar to that in normal plasma. Gammagard® is supplied lyophilized in 2.5, 5 or 10 g single use bottles. Each bottle of Gammagard® is furnished with a suitable volume of sterile water for
20 reconstitution.

In yet another preferred embodiment, pooled human immunoglobulin is purchased from the Bayer Corporation, where it is sold under the name Gamimune®. Gamimune® is a sterile solution of highly purified human
25 protein. Gamimune® contains 9-11% protein in 0.16-0.24 M glycine. At least about 90% of the protein is IgG monomer. Gamimune® also contains traces of IgA and IgM. The distribution of IgG subclasses is similar to that found in normal human serum. Gamimune® like Gammagard®
30 and Sandoglobulin® is made by cold ethanol fractionation of pools of human plasma obtained from thousands of volunteers.

In still another preferred embodiment, pooled human immunoglobulin is purchased from Centeon, L.L.C., where it is sold under the name Immune Globulin Intravenous (Human) Gammar®. Gammar® is a sterile solution of immunoglobulin, primarily immunoglobulin G (IgG), containing $16.5 \pm 15\%$ protein. Gammar® is prepared by cold alcohol fractionation of plasma pooled from at least 1000 donors. The pH of Gammar® is 6.8 ± 0.4 . Gammar® also contains approximately 0.45% sodium chloride, thimerosal, at a concentration of 0.01% and 0.3M glycine. The above-described pooled human immunoglobulin preparations are merely exemplary of the class of pooled human immunoglobulin preparations useful in accordance with the present invention.

In order to enhance the effectiveness of the introduced immunoglobulin in the treated patient and provide a clinically observable improvement, an antacid is administered in conjunction with the pooled immunoglobulin. In a preferred embodiment the immunoglobulin composition and the antacid are administered simultaneously in a unitary pharmaceutical composition. In another preferred embodiment the immunoglobulin composition is administered at a therapeutically effective time after administration of the antacid. Preferably, the antacid is aluminum hydroxide or magnesium hydroxide such as Maalox®, Mylanta® or Tagamet® which are available commercially. Most preferably the antacid is an H₂ blocker, such as Cimetidine or Ranitidine.

The dosage of antacid administered in conjunction with immunoglobulin depends on the particular H₂-blocker used. When the antacid is Mylanta®, between

15 ml and 30 ml is preferred. Most preferably the dosage of Mylanta® is 15 ml. When the cimetidine H2 blocker is used, the preferred dosage is between 400 and 800 mg per day.

5 The dosage of pooled human immunoglobulin administered to the patient may be varied dependent upon severity of the patient's arthritic condition and other clinical factors. Preferably, the dosage will be as small as possible while still providing a clinically
10 observable result. The most preferable doses are those that have the largest effect in terms of alleviating the patient's arthritic condition. Dosages of the immunoglobulin composition may range from as little as 100 mg per day up to as much as 10 g per day. Dosages of
15 1000 mg of pooled human immunoglobulin per day have been found to result in significant improvement in the condition of patients with rheumatoid arthritis and cause little or no adverse side effects. Accordingly, 1000 mg per day is a preferred dose.

20 Although the chosen dose may be given in increments, it also may be given as a single dose. Further, although the dose of immunoglobulin may be administered at any time during the day, it is preferred that it be administered in the morning, prior to
25 substantial patient activity.

 The patient's arthritic condition can be determined, for example, by the patient's self-assessment of his or her pain, stiffness, etc. Another way to determine the patient's arthritic condition is for a
30 physician to examine a patient's joint tenderness and swelling.

It is especially advantageous to formulate the pooled human immunoglobulin in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the rheumatoid arthritic subjects to be treated, each unit containing a predetermined quantity of pooled human immunoglobulin with or without an antacid calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifics for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the pooled human immunoglobulin, antacid and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a pooled human immunoglobulin for the treatment of adult rheumatoid arthritis herein disclosed in detail.

The pooled human immunoglobulin with or without an antacid is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the pooled human immunoglobulin in amounts ranging from about 100 mg to about 10 g and, if desired, an antacid in an amount ranging from about 400 to 800 mg.

Clinically observable results from the administration of immunoglobulin in conjunction with antacid may be observed in as little as 2 weeks. However, it may take up to 6 weeks to obtain measurable benefit. Initial dose levels used during the first few weeks of treatment may be reduced once clinical

improvement has been observed. Reductions in dose levels of up to 90% may be made after the first few weeks.

5 The oral treatment method in accordance with the present invention may be used to treat adult rheumatoid arthritis and other closely related autoimmune diseases such as spondyloarthopathies including but not limited to Ankylosing Spondylitis (AS), psoriatic arthritis, Reiter's Syndrome and the arthritis of inflammatory bowel disease including, but not limited to, 10 ulcerative colitis and Crohn's disease. The treatment of spondyloarthopathies according to the present invention would employ the same dosages as for rheumatoid arthritis and the same treatment protocol.

15 Demonstrations of the treatment of patients in accordance with the present invention are set forth in the following non-limiting examples.

EXAMPLE 1

5 An open-label study was conducted to evaluate the safety of oral gammaglobulin. Five patients were selected who had severe, unremitting rheumatoid arthritis unresponsive to conventional therapy. The patients continued to receive their prescribed medical regimen, and in addition were given 1 gram of encapsulated (uncoated) gammaglobulin daily in a single dose for six
10 weeks. There was no evidence of toxicity as a result of receiving oral gammaglobulin. Moreover, three of five patients showed improvement in the number of tender and swollen joints.

15 On the basis of the Phase I trial, a Phase II FDA approved double-blind placebo controlled trial was conducted in 28 patients with severe unresponsive rheumatoid arthritis to determine the efficacy of oral gammaglobulin in rheumatoid arthritis. Eight patients received 1 gram of uncoated gammaglobulin daily for 2
20 months, ten patients received 1 gram enteric coated gammaglobulin daily for 2 months, and 10 patients received a spite of optimum therapy with standard agents, including disease modifying anti-rheumatic drugs (DMARDs). Oral gammaglobulin was discontinued after 2
25 months, but the patients were followed for disease activity for an additional 2 months.

At the third month of observation 50% (4/8) of the patients treated with uncoated gammaglobulin fulfilled ACR criteria for 20% improvement compared to
30 11% of the placebo group (1/9) ($p < 0.05$).

The entire group of 18 patients treated with gammaglobulin showed a significant reduction in the

number of swollen joints. The improvement was observed at every follow-up visit compared to the initial visit with an overall reduction of about 40% by the third and fourth months ($p < 0.01$). In contrast, the placebo group
5 did not show a significant reduction of swollen joints at any time in the course of the study compared to the initial examination. Furthermore, 5 of the patients with markedly reduced joint swelling treated with
10 gammaglobulin showed at least 4-fold reductions in serum levels of C-reactive protein, rheumatoid factor, or both during the course of the study.

Patients in each study receiving 400 mg/day of the H_2 blocker, cimetidine were the best responders to oral gammaglobulin. There were no side affects
15 attributable to taking oral gammaglobulin in this study. The results of this study indicated that oral administration of gammaglobulin in conjunction with an H_2 blocker were effective in the treatment of rheumatoid
20 arthritis. The lack of toxicity indicated a favorable toxicity profile that made this treatment highly advantageous compared to other treatments or in combination with other treatments for rheumatoid
arthritis.

The following is a description of patients who
25 received both an H_2 blocker and oral immunoglobulin. These patients had the best clinical response. The patients improved more than 80%. Noticeably, the patients improved with respect to tender and swollen joints as well as physician's global assessment.

30 Patient #127, (CEG) a 75 year old Caucasian male with a history of sero-positive rheumatoid arthritis for 14 years. He was one patient in the placebo-

controlled double-blind study who took oral gammaglobulin in combination with cimetidine (400 mg/day). The patient was receiving a stable dose of cimetidine at the time the study was begun. This patient had clinically observable response. At the initial visit, he had 18 tender and 17 swollen joints. At the fourth visit, he had only 3 tender and swollen joints, or an improvement of 82%. The physician's initial global assessment was 8.0. At the fourth visit, the global assessment was 4.0. (Table I).

10

TABLE I

Patient ID: GEC Number 127

Month Number	Baseline	1	2	3	4
Number Tender Joints (Physician Assessment)	18		3	4	3
Number Swollen Joints (Physician Assessment)	17		10	10	3
Physician Total	35	ND	13	14	6

ND = not determined.

Patient No. 5, (RR) a 70 year old male with 12 year history of sero-positive rheumatoid arthritis with rheumatoid nodules. RR had severe uncontrolled disease almost exclusively involving his hands and wrists with erosions, deformities, and stiffness lasting all day. RR previously received gold therapy, but it was discontinued because of toxicity. RR was receiving methotrexate 15 mg/week, sulfasalazine 1 gm/day, Indocin® 25 mg at bedtime, Motrin® 1600 mg/day, Plaquenil® 400 mg/day, and Tagamet® 400 mg/day. Patient RR responded to oral immunoglobulin (given post-week 3) with clinically observable improvement, but flared two weeks after oral immunoglobulin was discontinued. (Table II).

TABLE II

Patient ID: R.R. Number 5

Week Number	0	1	2	3	4	5	6
A.M. Stiffness	all day	all day	all day	1	all day	4	0
Disability/Function	2	2	2	2	2	2	
Joint Tenderness (Number) (Patient Assessment)	12	6	8	7	6	4	4
Number Tender Joints (Physician Assessment)	19	3	9	6	4	1	2
Number Swollen Joints (Physician Assessment)	8	7	5	9	6	2	1
Physician Total	27	10	14	15	10	3	3

WHAT IS CLAIMED IS:

1. A method of treating adult autoimmune rheumatoid arthritis in a patient comprising orally administering to said patient an immunoglobulin composition comprising pooled human immunoglobulin in conjunction with a antacid in an amount sufficient to provide a clinically observable improvement in the rheumatoid arthritis of said patient.
2. The method of Claim 1 wherein said immunoglobulin composition comprises pooled human polyclonal IgG antibodies.
3. The method of Claim 2 wherein said immunoglobulin composition is selected from the group consisting of Sandoglobulin®, Gammagard® or Gamimune®.
4. The method of Claim 1 wherein said antacid is selected from the group consisting of aluminum hydroxide, magnesium hydroxide, cimetidine or ranitidine.
5. The method of Claim 1 wherein the amount of immunoglobulin composition which is administered to said patient is between 250 mg to 10 g per day.
6. The method of Claim 5 wherein the amount of immunoglobulin composition which is administered to said patient is about 1000 mg per day.
7. The method of Claim 1 wherein the amount of antacid which is administered to said patient is between 200 mg to 800 mg per day.

8. The method of Claim 7 wherein the amount of antacid which is administered to said patient is about 400 mg per day.

5 9. The method of Claim 1 wherein said immunoglobulin composition is administered in a unit dosage form.

10 10. The method of Claim 1 wherein said antacid is administered in a unit dosage form.

11. The method of Claim 1 wherein said immunoglobulin composition is in a powdered form.

15 12. The method of Claim 1 wherein said immunoglobulin composition is dispersed in pharmaceutically acceptable carrier.

20 13. The method of Claim 1 wherein said immunoglobulin composition and said antacid are administered simultaneously to said patient.

25 14. The method of Claim 1 wherein said immunoglobulin composition is administered at a therapeutically effective time after administration of said antacid.

30 15. A pharmaceutical composition comprising pooled human immunoglobulin, an antacid and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of Claim 15 wherein said pooled human immunoglobulin is Sandoglobulin®.

5 17. The pharmaceutical composition of Claim 15 wherein said antacid is cimetidine.

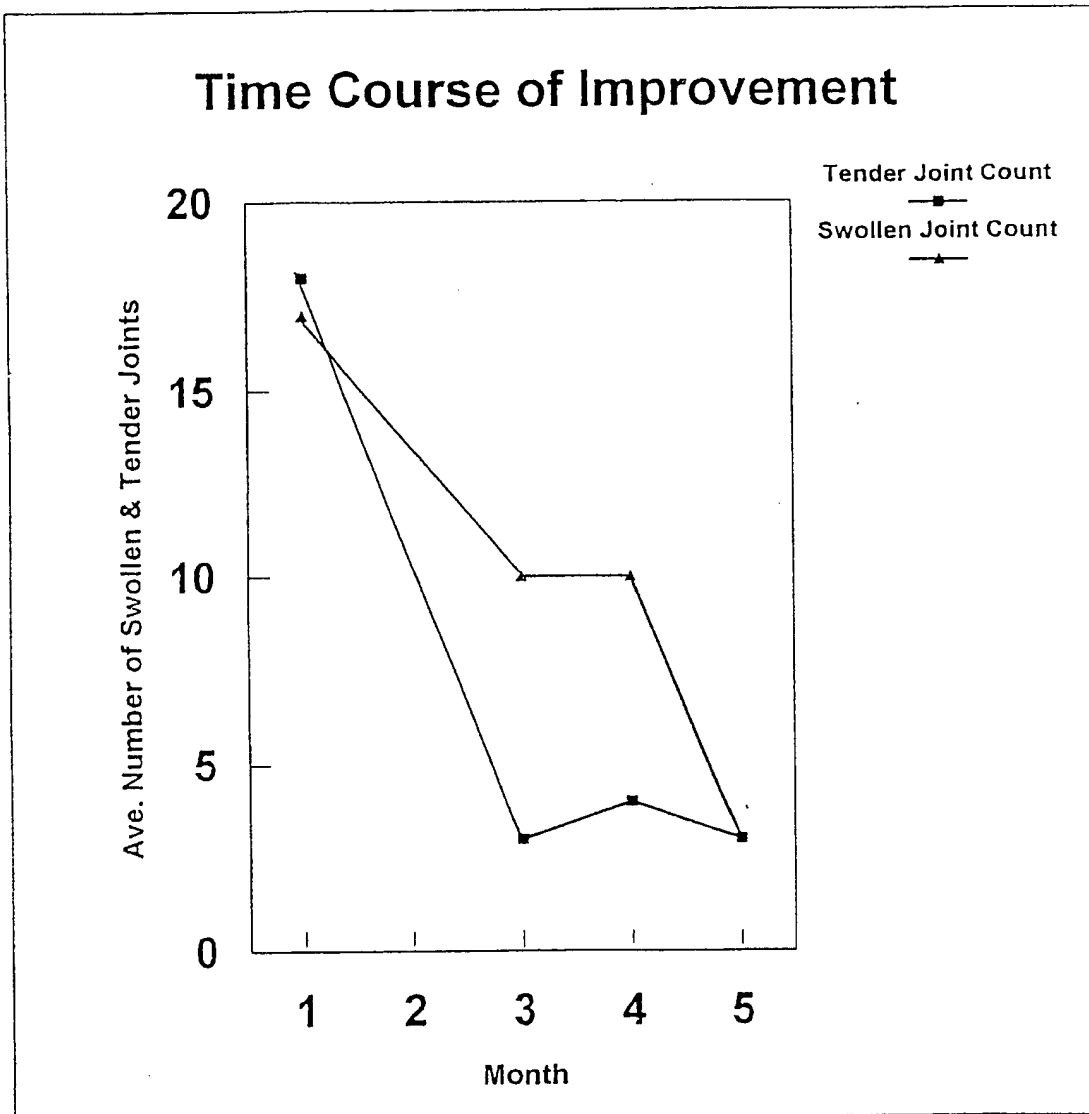


FIGURE 1

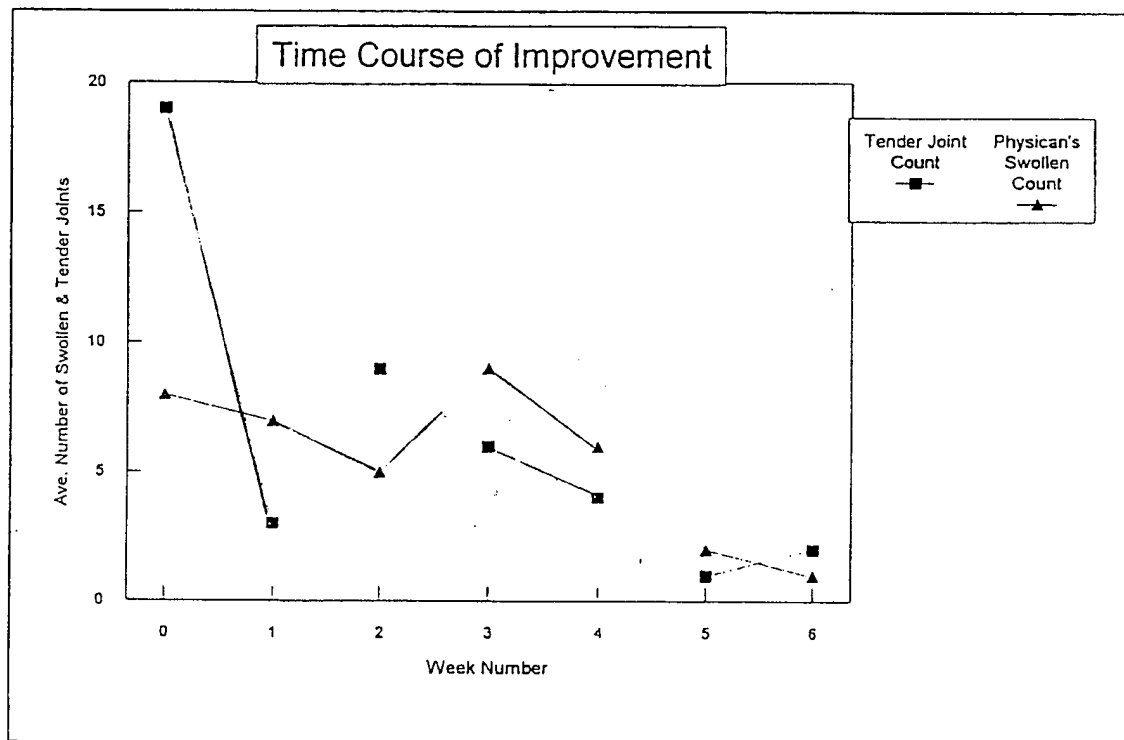


FIGURE 2

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/08578

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/395 //(A61K39/395, 31:34, 31:415, 33:06, 33:10)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 833 984 A (EIBL M ET AL) 10 November 1998 (1998-11-10) column 1, line 30 - line 35 column 4, line 25 - line 34 column 6, line 5 - line 7 column 6, line 46 - line 52 column 16, line 13 - line 17; claims 5,11	1,2, 4-15,17
Y	---	3,16
Y	GB 2 013 691 A (STOLLE RESEARCH AND DEVELOPMENT) 15 August 1979 (1979-08-15) claims 1-7 ---	3,16
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 December 1999

Date of mailing of the international search report

22/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Le Flao, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/08578

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 064 210 B (MILES LABORATORIES) 20 August 1986 (1986-08-20) column 2, line 51 - line 65 column 4, line 53 - line 59 column 6, line 59 -column 7, line 5; claims 1-4	15-17
A	GIANNINI E H ET AL: "Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis: a phase I/II study. Pediatric Rheumatology Collaborative Study Group 'see comments!." JOURNAL OF RHEUMATOLOGY, vol. 23, no. 5, May 1996 (1996-05), pages 919-24, XP000857451 abstract	1-17
A	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US AN97434949, 2 December 1997 (1997-12-02) PASHOV A ET AL: "A shift in encephalitogenic T cell cytokine pattern is associated with suppression of EAE by intravenous immunoglobulins (IVIg)." XP002124892 abstract & PASHOV A ET AL: "A shift in encephalitogenic T cell cytokine pattern is associated with suppression of EAE by intravenous immunoglobulins (IVIg)." MULTIPLE SCLEROSIS, vol. 3, no. 2, April 1997 (1997-04), pages 153-6,	1-17
A	MAKSYMOWYCH W P ET AL: "High dose intravenous immunoglobulin (IVIg) in severe refractory rheumatoid arthritis: no evidence for efficacy." CLINICAL AND EXPERIMENTAL RHEUMATOLOGY, vol. 14, no. 6, December 1996 (1996-12), pages 657-60, XP000857452 page 658, left-hand column, line 33 - line 35	1-17
A	FR 2 512 342 A (GLAXO GROUP) 11 March 1983 (1983-03-11) page 4, line 18 - line 21; claims 1-4	1-17

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/08578

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/08578

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5833984 A	10-11-1998	AT 402790 B	25-08-1997
		AT 29495 A	15-01-1997
		AT 182793 T	15-08-1999
		AU 1809495 A	04-09-1995
		CA 2183566 A	24-08-1995
		DE 19505287 A	24-08-1995
		DE 69511245 D	09-09-1999
		WO 9522350 A	24-08-1995
		EP 0744957 A	04-12-1996
		IT T0950112 A	18-08-1995
		JP 9509164 T	16-09-1997
GB 2013691 A	15-08-1979	CH 651210 A	13-09-1985
		DE 2904044 A	30-08-1979
		DK 49479 A,B,	07-08-1979
		FR 2416015 A	31-08-1979
		HK 30283 A	02-09-1983
		IT 1116524 B	10-02-1986
		JP 1060455 B	22-12-1989
		JP 1578209 C	13-09-1990
		JP 54113425 A	05-09-1979
		NL 7900766 A	08-08-1979
		SE 448344 B	16-02-1987
		SE 7900798 A	07-08-1979
		US RE33565 E	02-04-1991
		US 4732757 A	22-03-1988
EP 0064210 B	10-11-1982	EP 0064210 A	10-11-1982
		JP 1941158 C	23-06-1995
		JP 6069962 B	07-09-1994
		JP 57185222 A	15-11-1982
		US 4477432 A	16-10-1984
FR 2512342 A	11-03-1983	AU 564018 B	30-07-1987
		AU 8799782 A	10-03-1983
		BE 894285 A	02-03-1983
		CH 652304 A	15-11-1985
		CY 1398 A	18-12-1987
		DE 3232830 A	24-03-1983
		GB 2105193 A,B	23-03-1983
		HK 91387 A	11-12-1987
		IE 54149 B	05-07-1989
		IT 1208432 B	12-06-1989
		JP 58065215 A	18-04-1983
		KE 3739 A	04-09-1987
		MY 56087 A	31-12-1987
		NL 8203457 A	05-04-1983
		SE 8205034 A	03-09-1982
		SG 59387 G	23-10-1987
		ZA 8206477 A	25-04-1984